ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS OF PYRANO[2,3-c]PYRAZOLES

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Abstract - A novel synthesis of pyrano[2,3-c]pyrazoles is reported via reaction of β-phenylacrylonitrile with 3-methyl-2-pyrazolin-5-ones.

The considerable biological activities of fused pyrazoles in the past time have stimulated considerable research in this field.[1-3] In previous work from this laboratory we have reported several new and efficient approaches for the synthesis of fused azoles utilising laboratory available starting compounds.[4-7] In the present investigation we report a new procedure for the synthesis of pyrano-[2,3-c]pyrazoles via reaction of β-phenylacrylonitrile derivatives with 2-pyrazolin-5-ones. The synthesised compounds are interesting for biological activity studies and for utility in further chemical transformations.

Thus, in a typical procedure equimolecular amounts of 20 mmoles of the β-phenylacrylonitrile derivatives (1a-c) and 3-methyl-2-pyrazolin-5-one (2a) are refluxed in absolute ethanol (30 ml) in presence of piperidine (1 ml) for 20-180 minutes (TLC control). Removal of ethanol, trituration with water affords 1:1 adducts. Structure (3) could be established for these adducts based on the identity of the reaction products with the products obtained on refluxing 4-arylidene-3-methyl-2-pyrazolin-5-ones (4a-c) with malononitrile in presence of piperidine.

The behaviour of (4a-c) toward malononitrile finds parallelism to the reported behaviour of (4g) toward the same reagent.[8,9] Similarly (2a) reacted with the arylidenemalononitrile derivatives (5a-c) to yield the pyrano[2,3-c]pyrazole derivatives (6d-f). Compounds (6d-f) could be also synthesised from the reaction of malononitrile with the 4-arylidene-2-pyrazolin-5-one derivatives (4j-l).

Ethyl α-cyanocinnamate (1d) reacted with (2a) to yield the pyrano[2,3-c]-pyrazole derivatives (7a). Similarly (2a)reacted with (1e) to yield (7b).

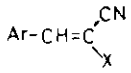
Table 1: List of the pyrano[2,3-c]pyrazole derivatives (3a-f), (6a-f), (7a-c), (8a-f) and pyrazole derivative (IX).

Compd.*	Reac. time (min)	M.p. (°C)	Yield (%)	Mol. Formul.	Compd.*	Reac. time (min)	M.p. (°C)	Yield (%)	Mol. Formul.
3a	15	242	94	$C_{14}H_{12}ON_4$	6f	120	182	80	$C_{26}H_{18}ON_4$
3b	120	206	85	$C_{15}H_{14}O_2N_4$	7a	120	120	72	$C_{14}H_{11}O_2N_3$
3c	120	212	82	$C_{14}H_{11}O_3N_5$	7b	120	123	69	$C_{20}H_{15}ON_3$
3d	20	175	71	$C_{20}H_{16}ON_4$	7c	180	174	52	$C_{26}H_{19}ON_3$
3e	20	185	72	$C_{21}H_{18}O_2N_4$	8a	20	165	60	$C_{20}H_{16}ON_4$
3f	20	184	75	$C_{20}H_{15}O_3N_5$	8b	20	204	82	$C_{21}H_{18}O_2N_4$
6a	120	320	66	$C_{20}H_{16}ON_4$	8c	20	229	76	$C_{20}H_{15}O_3N_5$
6b	120	140	74	$C_{22}H_{20}O_3N_4$	8d	120	275	80	$C_{26}H_{20}ON_4$
6c	120	239	70	$C_{20}H_{14}ON_4$	8e	120	141	76	$C_{28}H_{24}O_3N_4$
6d	60	136	70	$C_{26}H_{20}ON_4$	8f	120	210	86	$C_{26}H_{18}ON_4$
6e	60	141	74	$C_{28}H_{24}O_3N_4$	9	180	90	50	$C_{26}H_{19}ON_3$

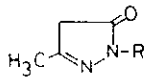
*Satisfactory elemental analyses for the newly synthesised compounds were obtained.

The formation of (7a,b) from reaction of (1d,e) and (2a) is assumed to proceed via initial Michael addition to yield acyclic Michael adducts which then cyclised via attack of the ring carbonyl either on the ester, benzoyl or cyano moieties. In our laboratories final isolable products resulting from attack at ester or -COPh moieties were obtained. Compounds (7a,b) were also obtained via the reaction of (4a) with ethyl cyanoacetate and benzoylacetonitrile respectively.

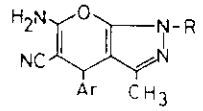
Compounds (1a-c) reacted with (2b) to yield 1:1 adducts. However, in contrast to the behaviour of (2a) these were found different from (3d-f) obtained via addition of malononitrile to the arylidene derivatives (4g-i). Moreover the IR spectra of these adducts revealed the absence of absorption for cyano groups and showed absorption for conjugately chelated NH groups. Based on ^{1}H NMR, structure (8) was suggested for these products. Thus, the ^{1}H NMR of all the reaction products revealed the vinyl-H at δ 8.16 ppm which is downfield shifted by the aniso-



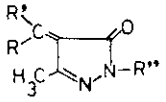
Ia, X=CN; Ar=Ph
b, X=CN; Ar=$C_6H_4OCH_3$-p
c, X=CN, Ar=$C_6H_4NO_2$-m
d, X=CO_2Et; Ar=Ph
e, X=COPh; Ar=Ph



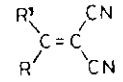
IIa, R = H
b, R = Ph



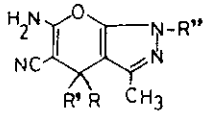
IIIa, R=H; Ar=Ph
b, R=H; Ar=$C_6H_4OCH_3$-p
c, R=H, Ar=$C_6H_4NO_2$-m
d, R=Ar=Ph
e, R=Ph, Ar=$C_6H_4OCH_3$-p
f, R=Ph, Ar=$C_6H_4NO_2$-m



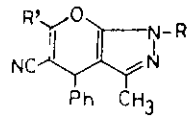
IVa, R=Ph; R'=R''=H
b, R=$C_6H_4OCH_3$-p; R'=R''=H
c, R=C_6H_4-NO_2-m; R'=R''=H
d, R=R'=Ph; R''=H
e, R=R'=$C_6H_4OCH_3$-p; R''=H
f, R+R'=9-fluorenylidenyl;
R''=H
g, R=R''=Ph, R'=H
h, R=$C_6H_4OCH_3$-p, R'=H, R''=Ph
i, R=$C_6H_4NO_2$-m, R'=H, R''=Ph
j, R=R'=R''=Ph
k, R=R'=$C_6H_4OCH_3$-p; R''=Ph
l, R+R'=9-fluorenylidenyl,
R''=Ph



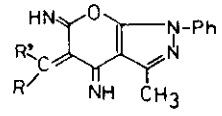
Va, R=R'=Ph
b, R=R'=$C_6H_4OCH_3$-p
c, R+R'=9-fluorenylidenyl



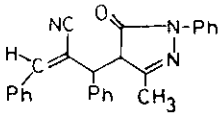
VIa, R=R'=Ph; R''=H
b, R=R'=$C_6H_4OCH_3$-p; R''=H
c, R+R'=9-fluorenylidenyl;
R''=H
d, R=R'=R''=Ph
e, R=R'=$C_6H_4OCH_3$-p; R''=Ph
f, R+R'=9-fluorenylidenyl;
R''=Ph



VIIa, R=H, R'=OH
b, R=H, R'=Ph
c, R=R'=Ph



VIIIa, R=Ph, R'=H
b, R=$C_6H_4OCH_3$-p; R'=H
c, R=$C_6H_4NO_2$-m; R'=H
d, R=R'=Ph
e, R=R'=$C_6H_4OCH_3$-p
f, R+R'=9-fluorenylidenyl



IX

tropy of the C=N linkage. The formation of (8) is assumed to proceed via addition of (2b) to the cyano group in (1a-c).

Similar to the behaviour of (1a-c) with (2b), the arylidenemalononitrile derivatives (5a-c) reacted with (2b) to yield the pyrano[2,3-c]pyrazole derivatives (8d-f). The isomers (6d-f) were obtained from the reaction of the arylidenepyrazolone derivatives (4j-l) with malononitrile.

Compound (1e) reacted with (2b) to yield (9). The structure of (9) was inferred from analytical and spectral data and nonidentity with a sample of isomeric (7c) prepared via reaction of (4g) with benzoylacetonitrile.

All procedures described were proved satisfactory. Several pyrano[2,3-c]-pyrazole derivatives with interesting synthetic and biological potentialities are now available. The behaviour of other heterocyclic derivatives toward (1a-e) is now under investigation. Also detailed investigation on the mechanism of these reactions is being undertaken. Work in progress will be the subject of a further communication.

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